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FORM PTO-1390 (REV 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 2499US0P

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/555949

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP98/05709	December 17, 1998	December 19, 1997

TITLE OF INVENTION: Phosphonocephem Derivatives, Their Production and Use

APPLICANT(S) FOR DO/EO/US: Tomoyasu ISHIKAWA et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)). *
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

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* This includes the Request and Specification 48 total pages, including Claims 1-28 and Abstract.

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/555949	PCT/JP98/05709	2499US0P

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	28	- 20 =	8	X **$18.00**	$ 144.00	
Independent claims	7	- 3 =	4	X **$78.00**	$ 312.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ **$260.00**	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =					$ 1,296.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$	
SUBTOTAL =					$ 1,296.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$	
TOTAL NATIONAL FEE =					$ 1,296.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$ 40.00	
TOTAL FEES ENCLOSED =					$ 1,336.00	
					Amount to be refunded:	$
					charged:	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 500799 in the amount of $ 1.336.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500799. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Philippe Y. Riesen

NAME
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REGISTRATION NUMBER
Date: June 2, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): T. ISHIKAWA et al.
Serial No. :
Filed on :
Title : Phosphonocephem Derivatives, Their Production and Use

Attn: Box PCT

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Preliminary to examination please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 35, delete lines 6-14

Page 37, delete lines 15-23

Page 37, line 24, delete "and talc)."

In the Claims:

Claim 11, page 45, line 6, delete "according to the above (1)" and substitute therefor --as claimed in claim 1--

Claim 12, page 45, line 7, delete "according to the above (1)" and substitute therefor --as claimed in claim 1--

Claim 13, page 45, line 11, delete "according to the above (1)" and substitute therefor --as claimed in claim 1--

Claim 21, page 46, line 27, delete "Use of" and substitute therefor --A method of using--

Claim 22, page 47, line 1, delete "Use of" and substitute therefor --A method of using--

Claim 23, page 47, line 3, delete "Use of" and substitute therefor --A method of using--

Claim 24, page 47, line 5, delete "Use of" and substitute therefor --A method of using--

REMARKS

The specification has been amended to correct typographical errors, specifically, to remove material that is duplicated

elsewhere in the specification. The claims have been amended to correct typographical errors. Early action on the merits is earnestly solicited.

Respectfully submitted,

Philippe Y. Riesen, Reg. No. 35,657
Miriam Sohn, Ph.D., Reg. No. 35,368
Attorney for Applicants

Customer No. 23,115

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Date: June 2, 2000

DESCRIPTION

Phosphonocephem Derivatives, Their Production and Use

TECHNICAL FIELD

This invention relates to a novel cephem compound having excellent antibacterial activities on a broad range of Gram-positive and Gram-negative bacteria, especially Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA) and a bacteria belonging to Pseudomonas and being sufficiently water-soluble, to a method of producing the compound and to a medicine, especially an antibacterial composition containing the compound.

BACKGROUND ART

Various cephem compounds having, at the 7-position, 2-(5-amino-1,2,4-thiadiazole-3-yl)-2(Z)-alkoxy-iminoacetamido group, and having, at the 3-position, 3-or 4-(pyridinium) thiazole-4-ylthio group or condensed heterocyclic ring-thio group containing N^+ as a ring constituting atom, have been reported in JPA H9(1997)-100283. However these compounds are not sufficiently soluble in water, and it is preferable to use solubilizing agents when these compounds are dissolved in water. Thus these compounds are not sufficiently satisfactory when they are used in a pharmaceutical preparation, especially for injection.

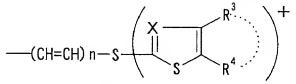
And various cephem compounds having, at the 7-position, 2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)-2(Z)-methoxyiminoacetamido group, and having at the 3-position, a substituted methyl, i.e., pyridiniummethyl group or 1-methylpyridiniumthiomethyl group which are different from substituted-$(CH=CH)_n$-S-group in chemical structure, have also been reported in JPA S59(1984)-31791.

Though some recently developed cephalosporin compounds have sufficient activity against methicillin-resistant Staphylococcus aureus (MRSA), they are poorly soluble in water or physiologically acceptable saline, which is necessary for

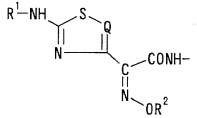
administration, and have not been put into practical use. Thus creation of novel compounds overcoming these problems has been desired.

DISCLOSURE OF INVENTION

Taking the foregoing circumstances into consideration, the present inventors diligently conducted extensive studies and synthesized, for the first time, a cephem compound characterized by having, at the 3-position of its cephem, oxacephem or carbacephem nucleus, a group of the formula:



wherein one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted; X is a nitrogen atom or CH; and n is 0 or 1, and, at the 7-position, a group of the formula:

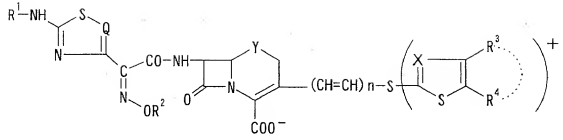


wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; Q is a nitrogen atom or CH, or an ester or salt thereof, and further found that the compound thus synthesized showed good solubility to water and has excellent medicinal properties such as antibacterial activity.

Based on these findings, the present invention was accomplished.

More specifically, the present invention relates to :

(1) A compound of the formula:



(1)

wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, salt or ester thereof;

(2) A compound according to the above (1), wherein R^1 is a phosphono group which may be protected;

(3) A compound according to the above (1), wherein R^1 is phosphono, dialkoxy-phosphoryl, O-alkyl-phosphono, diaminophosphoryl, (amino)(hydroxy)phosphoryl, (alkoxy)(morpholino)phosphoryl or dihalophosphoryl;

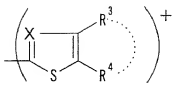
(4) A compound according to the above (1), wherein R^1 is a phosphono group;

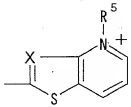
(5) A compound according to the above (1), wherein Y is S;

(6) A compound according to the above (1), wherein R^2 is a C_{1-6}alkyl group which may be substituted or a C_{3-5}cycloalkyl group;

(7) A compound according to the above (1), wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom;

(8) A compound according to the above (1), wherein


is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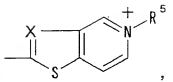
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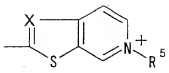
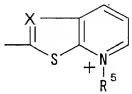


or



wherein R^5 is a hydrocarbon group which may be substituted;

(9) A compound according to the above (1), wherein Q is a nitrogen atom;

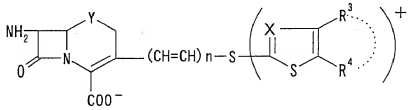
(10) A compound according to the above (1), wherein X is a nitrogen atom;

(11) A compound according to the above (1), wherein n is 0;

(12) A compound according to the above (1), which is 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester or its salt;

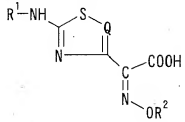
(13) A compound according to the above (1), which is 7β-[2(Z)-fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester or its salt;

(14) A method for producing a compound shown in the above (1) which comprises reacting a compound of the formula:


(II)

wherein each symbol has the meaning given above, its ester or its

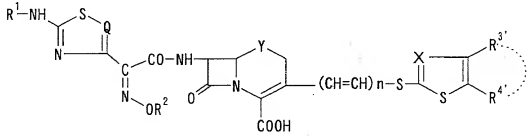
salt, with a compound of the formula:



(III)

wherein each symbol has the meaning given above, its salt or its reactive derivative, if necessary, followed by converting R^1 to a phosphono group;

(15) A method for producing a compound shown in the above (1) which comprises subjecting a compound of the formula:



(IV)

wherein one of $R^{3'}$ and $R^{4'}$ is a pyridyl group which may be substituted, and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or $R^{3'}$ and $R^{4'}$, taken together, represent a nitrogen-containing heterocyclic ring which may be substituted, and the other symbols have the meanings given above, its ester or its salt to the nitrogen quaternalization reaction in which quaternalized-ammonium is formed, if necessary, followed by converting R^1 to a phosphono group;

(16) A pharmaceutical composition containing the compound as shown in the above (1);

(17) A pharmaceutical composition containing the compound shown in the above (1) and at least one of pharmaceutically acceptable carriers, diluents and bulking agents;

(18) A pharmaceutical composition as shown in the above (16) which is an anti-bacterial composition;

(19) A pharmaceutical composition as shown in the above (16) which is an anti-MRSA agent;

(20) A pharmaceutical composition as shown in the above (16) which is an injectable composition;

(21) Use of the compound as shown in the above (1) for producing

a pharmaceutical composition;

(22) Use as shown in the above (21), wherein the pharmaceutical composition is an antibacterial agent;

(23) Use as shown in the above (21), wherein the pharmaceutical composition is an anti-MRSA agent;

(24) Use as shown in the above (21), wherein the pharmaceutical composition is an injectable composition;

(25) A method for treating a bacterial infection which comprises administering an effective amount of a compound as shown in the above (1) to a patient suffering from the bacterial infection;

(26) A method for treating a bacterial infection which comprises administering an effective amount of a compound as shown in the above (1) together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection;

(27) A method as shown in the above (25), wherein the bacterial infection is a MRSA infection;

and

(28) A method as shown in the above (25), wherein the compound is administered by injection.

BEST MODE FOR CARRYING OUT THE INVENTION

The cephem compound in the present specification includes a group of compounds named on the basis of "cepham" disclosed in "The Journal of The American Chemical Society" Vol. 84, p.3400 (1962), which means a compound, among the cepham compounds, having a double bond at the 3, 4-positions.

Incidentally, the compounds of this invention include the compound of the formula (I) showing the free form or an ester or salt thereof (a salt of the compound (I) or a salt of the ester of the compound (I)). In the present specification, hereinafter, unless otherwise specified, the compound of the formula (I) shown in the free form or an ester or salt thereof is simply referred to as the compound (I) or the antibacterial compound (I). Accordingly, the compound (I) in the present specification includes, usually, the free form as well as an ester or salt thereof.

R^1 is a phosphono group or a group convertible to a phosphono group. The group convertible to a phosphono group is a group which can be converted to a phosphono group, for example, by hydrolysis, substitution reaction, etc. Examples of the group convertible to phosphono group include, for example, dihalophosphoryl such as di-chlorophosphoryl, etc. in addition to a protected-phosphono group.

The protected-phosphono group is a phosphono group protected by a phosphono-protective group. In the field of nucleic acid, phosphono-protective groups have been sufficiently studied, and the method of a protecting phosphono group has been established. In the present invention also, conventional phosphono-protective groups can be adequately employed. Examples of protected-phosphono groups include mono-or di-ester phosphono group (e.g., dihalophosphoryl such as di-chlorophosphoryl, etc.; dialkoxy-phosphoryl group such as di-methoxyphosphoryl, di-ethoxyphosphoryl, di-propoxyphosphoryl, etc.; O-alkyl-phosphono group such as O-methyl phosphono, O-ethyl phosphono, etc.), mono-esterified mono-amidated phosphono group (e.g., mono-or di-amidated phosphono group such as diaminophosphoryl, (amino)(hydroxy)phosphoryl, etc.; (alkoxy)(amino)phosphoryl group such as (methoxy)(amino)phosphoryl, (ethoxy)(amino)phosphoryl, etc.; (alkoxy)(morpholino)phosphoryl group such as (methoxy)(morpholino)phosphoryl, (ethoxy)(morpholino)phosphoryl, etc.), etc. As R^1, phosphono, dialkoxy-phosphoryl, O-alkyl-phosphono, diaminophosphoryl, (amino)(hydroxy)phosphoryl, (alkoxy)(morpholino)phosphoryl or dihalophosphoryl are preferable, and phosphono is the most preferable.

R^2 is a hydrogen atom or a group having a linkage through a carbon atom. Examples of the group having a linkage through a carbon atom represented by R^2 include, for example, a hydrocarbon group which may be substituted (for example, an alkyl group which may be substituted, an alkenyl group which may be substituted, an alkynyl group which may be substituted, an aralkyl group which may be substituted, a cyclic hydrocarbon group which may be

substituted), an acyl group or a non-aromatic heterocyclic group (having linkage at a carbon atom) which may be substituted. Among them, an alkyl group which may be substituted, an alkenyl group which may be substituted, a cyclic hydrocarbon group which may be substituted etc. are preferable. As the alkyl group in "an alkyl group which may be substituted", a C_{1-6}alkyl group, etc., are preferable, and methyl, ethyl, isopropyl, etc. are the most preferable. As the alkenyl group in "an alkenyl group which may be substituted", a C_{2-6}alkenyl group is preferable. As the alkynyl group in "an alkynyl group which may be substituted", a C_{2-6}alkynyl group is preferable. As the aralkyl group in "an aralkyl group which may be substituted", a C_{7-20}aralkyl group is preferable. Examples of the cyclic hydrocarbon group in "a cyclic hydrocarbon group which may be substituted" include, a 3 to 7 membered non-aromatic cyclic hydrocarbon group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclopentene-1-yl, 3-cyclopentene-1-yl, 2-cyclohexene-1-yl, 3-cyclohexene-1-yl, etc., etc. Among them, a C_{3-7}cycloalkyl group such as cyclobutyl, cyclopentyl, etc. are preferable. Examples of the acyl group include, for example, a C_{1-6}alkanoyl group which may be substituted, a C_{3-5}alkenoyl group which may be substituted, a C_{6-10}aryl-carbonyl group which may be substituted, a heterocyclic carbonyl group, etc.

As the "optionally substituted C_{1-6}alkanoyl group", use is made of, for example, a C_{1-6}alkanoyl group which may optionally be substituted with 1 to 3 substituents selected from a halogen, oxo, a C_{1-6}alkoxy, a C_{1-6}alkanoyl, a C_{6-10}aryl, a C_{6-10}aryloxy, and a C_{6-10}arylthio. More specifically, use is made of, for example, formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, monochloroacetyl, dichloroacetyl, trichloroacetyl, monobromoacetyl, monofluoroacetyl, difluoroacetyl, trifluoroacetyl, monoiodoacetyl, acetoacetyl, 3-oxobutyryl, 4-chloro-3-oxobutyryl, phenylacetyl, p-chlorophenylacetyl, phenoxyacetyl and p-chlorophenoxyacetyl.

As the "optionally substituted C_{3-5}alkenoyl group", use is made of, for example, a C_{3-5}alkenoyl group optionally substituted

with 1 to 3 substituents selected from a halogen and a C_{6-10}aryl, more specifically, for example, acryloyl, crotonoyl, maleoyl, cinnamoyl, p-chlorocinnamoyl and β-phenylcinnamoyl.

As the "optionally substituted C_{6-10}aryl-carbonyl group", use is made of, for example, a C_{6-10}aryl-carbonyl group optionally substituted with 1 to 3 substituents selected from a halogen, nitro, hydroxy, a C_{1-6}alkyl and a C_{1-6}alkoxy, more specifically, for example, benzoyl, naphthoyl, phthaloyl, p-toluoyl, p-tert-butylbenzoyl, p-hydroxybenzoyl, p-methoxybenzoyl, p-tert-butoxybenzoyl, p-chlorobenzoyl and p-nitrobenzoyl.

The "heterocyclic group" in "heterocyclic carbonyl group" means a group formed by removing one hydrogen atom linked to carbon atom of the heterocyclic ring. The heterocyclic ring means a 5-to 8-membered ring containing 1 to several, preferably 1 to 4 hetero-atoms such as a nitrogen atom which may be oxidized, oxygen atom and a sulfur atom, or a condensed ring thereof. As such a heterocyclic group, for example, 2-or 3-pyrrolyl; 3-, 4-or 5-pyrazolyl; 2-, 4-or 5-imidazolyl; 1,2,3-or 1,2,4-triazolyl; 1H-or 2H-tetrazolyl; 2-or 3-furyl; 2-or 3-thienyl; 2-, 4-or 5-oxazolyl; 3, 4-or 5-isoxazolyl; 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,5-or 1,3,4-oxadiazolyl; 2-, 4-or 5-thiazolyl; 3-, 4-or 5-isothiazolyl; 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,2,5-or 1,3,4-thiadiazolyl; 2-or 3-pyrrolidinyl; 2-, 3-or 4-pyridyl; 2-, 3-or 4-pyridyl-N-oxido; 3-or 4-pyridazinyl; 3-or 4-pyridazinyl-N-oxido; 2-, 4-or 5-pyrimidinyl; 2-, 4-or 5-pyrimidinyl-N-oxido; pyrazinyl; 2-, 3-or 4-piperidinyl; piperazinyl; 3H-indol-2-yl or 3H-indol-3-yl; 2-, 3-or 4-pyranyl; 2-, 3-or 4-thiopyranyl; benzopyranyl; quinolyl; pyrido[2,3-d]pyrimidyl; 1,5-, 1,6-, 1,7-, 1,8-, 2,6-or 2,7-naphthyridyl; thieno[2,3-d]pyridyl; pyrimidopyridyl; pyrazinoquinolyl; and benzopyranyl can be used.

Examples of the non-aromatic heterocyclic group in "a non-aromatic heterocyclic group having a linkage at a carbon atom, which may be substituted" preferably include a 3 to 6 membered non-aromatic heterocyclic group containing 1 or 2 hetero atoms

such as a nitrogen atom, an oxygen atom, a sulfur atom in addition to a carbon atom, such as oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl.

Examples of the substituents, which the above-mentioned "hydrocarbon group" may optionally have, include a heterocyclic group, a hydroxyl group, a C_{1-6}alkoxy group, a C_{3-10}cycloalkyl group, a C_{3-7}cycloalkyloxy group, a C_{6-10}aryloxy group, a C_{7-19}aralkyloxy group, a heterocyclic-oxy group, a mercapto group, a C_{1-6}alkylthio group, a C_{3-10}cycloalkylthio group, a C_{6-10}arylthio group, a C_{7-19}aralkylthio group, a heterocyclic-thio group, an amino group, a mono-C_{1-6}alkylamino group, a di-C_{1-6}alkylamino group, a tri-C_{1-6}alkyl ammonium group, a C_{3-10}cycloalkylamino group, a C_{6-10}arylamino group, a C_{7-19}aralkylamino group, a heterocyclic amino group, a cyclic amino group, an azido group, a nitro group, a halogen atom, a cyano group, a carboxyl group, a C_{1-10}alkoxy-carbonyl group, a C_{1-10}aryloxy-carbonyl group, a C_{7-19}aralkyloxy-carbonyl group, a C_{6-10}aryl-carbonyl group, a C_{1-6}alkanoyl group, a C_{3-5}alkenoyl group, a C_{6-10}aryl-carbonyloxy group, a C_{2-6}alkanoyloxy group, a C_{3-5}alkenoyloxy group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted carbamoyloxy group, a phthalimido group, a C_{1-6}alkanoylamino group, a C_{6-10}aryl-carbonylamino group, a C_{1-10}alkoxy-carboxamido group, a C_{6-10}aryloxy-carboxamido group and a C_{7-19}aralkyloxy-carboxamido group. The number of these substituents, which may be the same as or different from one another, ranges from 1 to 4.

Among specific examples of the above-mentioned substituents of the "hydrocarbon group", as the "optionally substituted carbamoyl group", use is made of, for example, a carbamoyl group and a cyclic aminocarbonyl group optionally substituted with one or two substituents selected from, for example, a C_{1-6}alkyl group, a C_{6-10}aryl group, a C_{1-6}alkanoyl group, a C_{6-10}arylcarbonyl group and a C_{1-6}alkoxy-phenyl group. More specifically, use is made of, for example, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-

phenylcarbamoyl, N-acetylcarbamoyl, N-benzoylcarbamoyl, N-(p-methoxyphenyl)carbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, piperazinocarbonyl and morpholinocarbonyl. As the "optionally substituted thiocarbamoyl group", use is made of a thiocarbamoyl group optionally substituted with one or two substituents selected from, for example, a C_{1-6}alkyl group and a C_{6-10}aryl group, which are exemplified by thiocarbamoyl, N-methylthiocarbamoyl and N-phenylthiocarbamoyl. As the "optionally substituted carbamoyloxy group", use is made of a carbamoyloxy group optionally substituted with one or two substituents selected from, for example, a C_{1-6}alkyl group and a C_{6-10}aryl group. Specific examples include carbamoyloxy, N-methyl carbamoyloxy, N,N-dimethyl carbamoyloxy, N-ethyl carbamoyloxy and N-phenyl carbamoyloxy.

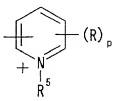
As the heterocyclic group and the heterocyclic group in the heterocyclic-oxy group, the heterocyclic-thio group and the heterocyclic amino group in the substituent of the "hydrocarbon group", use is made of group similar to those in the "heterocyclic carbonyl group" as mentioned above.

Examples of the substituent in the "non-aromatic heterocyclic group having a linkage at a carbon atom, which may be substituted" mentioned above include the embodiments mentioned as the hydrocarbon group and its substituent in the "hydrocarbon group which may be substituted".

As R^2, an optionally substituted hydrocarbon group is preferable. Examples of the "optionally substituted hydrocarbon group" shown by R^3 include a C_{1-6}alkyl group optionally substituted with one to three substituents selected from, for example, a hydroxyl group, a C_{3-10}cycloalkyl group, a C_{1-6}alkoxy group, a C_{1-6}alkylthio group, an amino group, a halogen atom, carboxyl group, a C_{1-10}alkoxycarbonyl group, an optionally substituted carbamoyl group, a cyano group, an azido group and a heterocyclic group, which are more specifically exemplified by cyclopropylmethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-hydroxyethyl, methylthiomethyl, 2-aminoethyl, fluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, chloromethyl, 2-chloroethyl, 2,2-

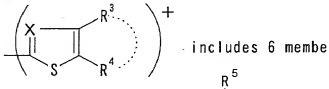
dichloroethyl, 2,2,2-trichloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trifluoroethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 2-carboxypropyl, 3-carboxypropyl, 1-carboxybutyl, cyanomethyl, 1-carboxy-1-methylethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonyl-1-methylethyl, 1-ethoxycarbonyl-1-methylethyl, 1-tert-butoxycarbonyl-1-methylethyl, 1-benzyloxycarbonyl-1-methylethyl, 1-pivaloyloxycarbonyl-1-methylethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-azidoethyl, 2-(pyrazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(2-oxopyrrolidin-3-yl)ethyl and 1-carboxyl-1-(2,3,4-trihydroxyphenyl)methyl. Most preferable examples of R^2 include, for example, a straight chain or branched C_{1-6}alkyl group which may be substituted with one to three substituents selected from a halogen, a hydroxyl group, a C_{1-6}alkoxy group, a carboxyl group, a C_{1-10}alkoxy-carbonyl group, a cyano group, a carbamoyl group and a substituted carbamoyl, such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, fluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, etc., a C_{3-5}cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, etc. and a C_{3-5}cycloalkyl-C_{1-3}alkyl group such as cyclopropylmethyl, etc. Among them, a C_{1-6}alkyl group which may be substituted and C_{3-5}cycloalkyl group are preferable.

One of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4, taken together, represent a heterocyclic group which may be substituted containing a quaternalized nitrogen. Examples of the "pyridinium group which may be substituted" include, for example, a group of the formula:

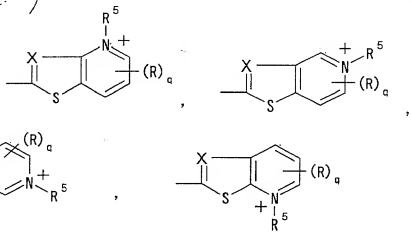


wherein R^5 is a hydrocarbon group which may be substituted, R is a C_{1-6}alkyl group, a C_{1-6}alkoxy group, a C_{1-6}alkoxy-carbonyl group, a amino group, a nitro group, a halogen atom or a carboxy group, p is an integer of from 0 to 4, etc.

In case that R^3 and R^4, taken together, represent a heterocyclic group containing a quaternalized nitrogen, which may be substituted, the group of the formula:



includes 6 membered unsaturated heterocyclic groups such as



wherein q is an integer of 0 to 3, and the other symbols have the meanings given above, etc.

Examples of the "hydrocarbon group which may be substituted" represented by R^3, R^4 or R^5 include those mentioned in the explanation of "a group having a linkage through a carbon atom" represented by R^2.

Each of p and q is preferably 0.

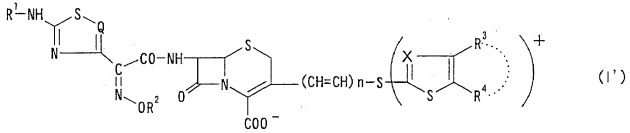
R^5 is preferably is a C_{1-4}alkyl group such as methyl, etc.

Referring to R^3 and R^4, it is preferable that R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom, or that R^3 and R^4, taken together, represent a 6 membered unsaturated heterocyclic group having a quaternalized nitrogen atom.

Each of Q and X is a nitrogen atom or CH. Each of Q and X is

preferably a nitrogen atom.

Y is S, O or CH_2. Y is preferably S. That is, among the compound (I), a compound of the formula:



(I')

wherein each symbol has the meaning given above, its ester or its salt is preferable. While n can be 0 or 1, it is preferably 0.

In the above-mentioned compound (I), the mark [-] attached on the right shoulder of-COO at the 4-position shows that the carboxyl group forms carboxylate anion, making a pair with the positive charge on the pyridine ring (hereinafter sometimes simply referred to as A^+). On the other hand, the compound (I) may optionally form a pharmaceutically acceptable ester or salt. As the pharmaceutically acceptable salt, use is made of, for example, inorganic basic salts, ammonium salts, organic basic salts, inorganic acid addition salts, organic acid addition salts and basic amino acid salts. As the inorganic base capable of forming the inorganic basic salt, use is made of, for example, alkali metal (e.g. sodium and potassium) and alkaline earth metals (e.g. calcium); as the organic base capable of forming the organic basic salt, use is made of, for example, procaine, 2-phenylethyl benzylamine, dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane, polyhydroxyalkylamine and N-methylglucosamine; as an inorganic acid capable of forming the inorganic acid addition salt, use is made of, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; as an organic acid capable of forming the organic acid addition salt, use is made of, for example, p-toluenesulfonic acid, methanesulfonic acid, formic acid, trifluoroacetic acid and maleic acid; and, as a basic amino acid capable of forming the basic amino acid salt, use is made of, for example, lysine, arginine, ornithine and histidine. Among these salts, a basic salt (i.e. an inorganic basic salt,

an ammonium salt, an organic basic salt and a basic amino acid salt) means that capable of being formed in the case where a basic group such as amino group, a monoalkylamino group, a dialkylamino group, a cycloalkylamino group, an arylamino group, an aralkylamino group, a cyclic amino group and a N-containing heterocyclic group exists in the substituent R^1, R^2 or R^5 of the compound (I). And, examples of the acid addition salt include a salt in which the substituent at 4-position is a carboxyl group (COOH) and the substituent at 3-position is-$(CH=CH)_n$-S-A^+Z^- [wherein Z^-stands for anion formed by removing proton H^+ from the inorganic acid or the organic acid, the anion being exemplified by a chloride ion, a bromide ion, a sulfate ion, a p-toluenesulfonate ion, a methanesulfonate ion and a trifluoroacetate ion, etc.] the salt being formed by adding one mole of acid to the moiety forming the internal salt of the compound (I), i.e. the carboxylate moiety (COO^-) at the 4-position and heterocyclic ring moiety at the 3-position. The ester derivative of the compound (I) means an ester producible by esterifying the carboxyl group in the molecule which is utilizable as an intermediate of the synthesis and is metabolically unstable and a non-toxic ester. Examples of the ester utilizable as intermediate of the synthesis include an optionally substituted C_{1-6}alkyl ester, a C_{2-6}alkenyl ester, a C_{3-10}cycloalkyl ester, a C_{3-10}cycloalkyl-C_{1-6}alkyl ester, an optionally substituted C_{6-10}aryl ester, an optionally substituted C_{7-12}aralkyl ester, a di-C_{6-10}aryl-methyl ester, a tri-C_{6-10}aryl-methyl ester, a substituted silyl ester and a C_{2-6}alkanoyloxy-C_{1-6}alkyl ester.

As the "optionally substituted C_{1-6}alkyl ester", use is made of, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl, which may be substituted with one to three of, for example, benzyloxy, a C_{1-4}alkyl sulfonyl (e.g. methyl sulfonyl), trimethylsilyl, a halogen (e.g. fluorine, chlorine and bromine), acetyl, nitrobenzoyl, mesylbenzoyl, phthalimido, succinimide, benzenesulfonyl, phenylthio, a di-C_{1-4}alkylamino (e.g. dimethylamino), pyridyl, a C_{1-4}alkyl sulfinyl (e.g. methyl sulfinyl) and cyano. Examples of such groups include

benzyloxymethyl, 2-methylsulfonylethyl, 2-trimethylsilylethyl, 2,2,2-trichloroethyl, 2-iodoethyl, acetylmethyl, p-nitrobenzoylmethyl, p-mesylbenzoylmethyl, phthalimidomethyl, succinimidomethyl, benzenesulfonylmethyl, phenylthiomethyl, dimethylaminoethyl, pyridine-oxido-2-methyl, methylsulfinylmethyl and 2-cyano-1,1-dimethylethyl.

As the C_{2-6}alkenyl group forming the "C_{2-6}alkenyl ester", use is made of, for example, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethylallyl and 3-methyl-3-butenyl.

As the C_{3-10}cycloalkyl group forming the "C_{3-10}cycloalkyl ester", use is made of, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl and adamantyl.

As the C_{3-10}cycloalkyl-C_{1-6}alkyl group forming the "C_{3-10}cycloalkyl-C_{1-6}alkyl ester", use is made of, for example, cyclopropylmethyl, cyclopentylmethyl and cyclohexylmethyl.

As the "C_{6-10}aryl group" forming the "optionally substituted C_{6-10}aryl ester", use is made of, for example, phenyl, α-naphthyl, β-naphthyl and biphenylyl, which may optionally be substituted with one to three of, for example, nitro and a halogen (e.g. fluorine, chlorine and bromine). The above group is specifically exemplified by p-nitrophenyl and p-chlorophenyl.

As the "C_{7-12}aralkyl group" forming the "optionally substituted C_{7-12}aralkyl ester", use is made of, for example, benzyl, 1-phenylethyl, 2-phenylethyl, phenylpropyl and naphthylmethyl, which may optionally be substituted with one to three of, for example nitro, a C_{1-4}alkoxy (e.g. methoxy), a C_{1-4}alkyl (e.g. methyl and ethyl) and hydroxy. Specific examples of such group include p-nitrobenzyl, p-methoxybenzyl and 3,5-di-tert-butyl-4-hydroxybenzyl.

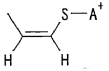
As the di-C_{6-10}aryl-methyl group forming the "di-C_{6-10}aryl-methyl ester", use is made of, among others, benzhydryl; as the tri-C_{6-10}aryl-methyl group forming the tri-C_{6-10}aryl-methyl ester, use is made of, among others, trityl; as the substituted silyl group forming the substituted silyl ester, use is made of, for example, trimethylsilyl, tert-butyldimethylsilyl and-

$Si(CH_3)_2CH_2CH_2Si(CH_3)_2$-. As the C_{2-6}alkanoyloxy-C_{1-6}alkyl ester, use is made of, for example, acetoxymethyl ester. Examples of the above-mentioned ester include an ester at 4-position. The compound, wherein the substituent at 4-position is the above-mentioned ester group, forms a salt in which the substituent at 3-position is-$(CH=CH)_n$-S-A^+Z^-[wherein symbols are of the same meaning as defined above].

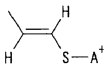
The present invention includes, besides the above-described ester derivatives, pharmacologically acceptable compounds convertible into the compound (I) in vivo.

The compound (I) and starting compounds of this invention, in case that n is 1, include cis-isomer (Z-compound), trans-isomer (E-compound) and a cis-trans mixture. The compound (I) of this invention is preferably a trans-isomer (E-compound).

Referring to the compound (I), the cis-isomer (Z-compound), for example, means one of the geometrical isomers having the partial structure represented by the formula:



, and the trans-isomer means a geometrical isomer having the partial structure of the formula:



Among the compound (I), for example, 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester, its salt, 7β-[2(Z)-fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester and its salt, are especially preferable.

In the present specification, specific examples of the respective substituents are, unless specifically described, as follows.

halogen : fluoro, chloro, bromo, iodo, etc.;

C_{1-4}alkyl group : methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, etc.;

C_{1-6}alkyl group : the above mentioned C_{1-4}alkyl group and pentyl, 2,2-dimethyl propyl, hexyl, etc.;

C_{2-6}alkenyl group : vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethyl allyl, etc.;

C_{2-6}alkynyl group : ethynyl, 1-propynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 2-hexynyl, etc.;

C_{3-5}cycloalkyl group : cyclopropyl, cyclobutyl, cyclopentyl, etc.;

C_{3-10}cycloalkyl group : the above mentioned C_{3-5}cycloalkyl group and cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, etc.;

C_{6-10}aryl group : phenyl, naphthyl, etc.;

C_{7-20}aralkyl group : benzyl, 1-phenyl ethyl, 2-phenyl ethyl, phenyl propyl, naphthyl methyl, benzhydryl, etc.;

C_{1-6}alkoxy group : methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, 2,2-dimethyl propyloxy, hexyloxy, etc.;

C_{3-7}cycloalkyloxy group : cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.;

C_{6-10}aryloxy group : phenoxy, naphthyloxy, etc.;

C_{7-19}aralkyl-oxy group : benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, benzhydryloxy, etc.;

C_{1-6}alkyl-thio group : methylthio, ethylthio, propylthio, butylthio, isobutylthio, t-butylthio, pentylthio, 2,2-dimethylpropylthio, hexylthio, etc.;

C_{3-10}cycloalkyl-thio group : cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cycloheptylthio, cyclooctylthio, cyclodecylthio, etc.;

C_{6-10}aryl-thio group : phenylthio, naphthylthio, etc.;

C_{7-19}aralkyl-thio group : benzylthio, phenylethylthio, benzhydrylthio, tritylthio, etc.;

C_{1-4}alkyl-sulfinyl group : methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, t-

butylsulfinyl, etc.;

C_{1-4}alkyl-sulfonyl group : methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, t-butylsulfonyl, etc.;

mono-C_{1-6}alkyl-amino group : methylamino, ethylamino, n-propylamino, n-butylamino, etc.;

di-C_{1-4}alkyl-amino group : dimethylamino, diethylamino, methylethylamino, di-(n-propyl)amino, di-(n-butyl)amino, etc.;

di-C_{1-6}alkyl-amino group : the above mentioned di-C_{1-4}alkyl amino group and di-(pentyl)amino, di-(n-hexyl)amino, etc.;

tri-C_{1-6}alkyl-ammonium group : trimethylammonium, etc.;

C_{3-10}cycloalkyl-amino group : cyclopropylamino, cyclopentylamino, cyclohexylamino, etc.;

C_{6-10}aryl-amino group : anilino, N-methylanilino, etc.;

C_{7-19}aralkyl-amino group : benzylamino, 1-phenylethylamino, 2-phenylethyl amino, benzhydrylamino, etc.;

Cyclic amino group : pyrrolidino, piperidino, piperazinyl, morpholino, 1-pyrrolyl, etc.;

C_{1-6}alkanoyl amino group : acetamido, propionamido, butyroamido, valeroamido, pivaloamido, etc.;

C_{6-10}aryl-carbonyl amino group : benzamido, naphthoylamido, phthalimide, etc.;

C_{1-6}alkanoyl group : formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, etc.;

C_{2-6}alkanoyloxy group : acetoxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy, etc.;

C_{3-5}alkenoyl group : acryloyl, crotonoyl, maleoyl, etc.;

C_{3-5}alkenoyl-oxy group : acryloyloxy, crotonoyloxy, maleoyloxy, etc.;

C_{6-10}aryl-carbonyl group : benzoyl, naphthoyl, phthaloyl, phenyl acetyl, etc.;

C_{6-10}aryl-carbonyloxy group : benzoyloxy, naphthoyloxy, phenylacetoxy, etc.;

C_{1-6}alkoxy-phenyl group : methoxyphenyl, ethoxyphenyl, propoxyphenyl, butoxy phenyl, t-butoxyphenyl, etc.;

C_{1-10}alkoxy-carbonyl group : methoxycarbonyl, ethoxycarbonyl,

propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, 2,2-dimethylpropyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, decyloxycarbonyl, etc.;

C_{2-10}alkenyloxy-carbonyl group : allyloxycarbonyl, etc.;

C_{6-10}aryloxy-carbonyl group : phenoxycarbonyl, naphthyloxycarbonyl, etc.;

C_{7-19}aralkyl-oxycarbonyl group : benzyloxycarbonyl, benzhydryloxycarbonyl, etc.;

C_{1-10}alkoxy-carboxamido group : methoxycarboxamido (CH_3OCONH-), ethoxycarboxamido, tert-butoxycarboxamido, etc.;

C_{6-10}aryloxy-carboxamido group : phenoxycarboxamido (C_6H_5OCONH-), etc.

Methods of producing the compound (I) of this invention are hereinafter described in detail.

Production method (1) :

The compound (I) can be synthesized by allowing, for example, a compound of the formula (II) or an ester or salt thereof (hereinafter referred to as Compound (II)) to react with a compound of the formula (III) or its salt or a reactive derivative thereof (hereinafter referred to as Compound (III)), followed by removing the protective group so as to change the group R^1 to a phosphono group.

The present method is to acylate a compound (II) by using compound (III). Compound (II) can be used as it is, and can also be used as its salt or its ester.

Examples of the salts of Compound (II) include an inorganic basic salt, an ammonium salt, an organic basic salt, an inorganic acid addition salt and an organic acid addition salt. Examples of inorganic basic salts include an alkali metal salt (e.g. sodium salt and potassium salt) and an alkaline earth metal salt (e.g. calcium salt); examples of an organic basic salt include trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt and quinoline salt; examples of the inorganic acid addition salts include hydrochloride, hydrobromide, sulfate, nitrate and

phosphate; and examples of the organic acid addition salts include formate, acetate, trifluoroacetate, methanesulfonate and p-toluenesulfonate.

As the ester of amino compound (II), mention is made of esters already described as the ester derivatives of compound (I), as exemplified by, more specifically, a C_{1-6}alkyl ester, a C_{2-6}alkenyl ester, a C_{3-10}cycloalkyl ester, a C_{3-6}cycloalkyl-C_{1-6}alkyl ester, a C_{6-10}aryl ester, a C_{7-12}aralkyl ester, a di-C_{6-10}arylmethyl ester, a tri-C_{6-10}arylmethyl ester and a C_{2-6}alkanoyloxy-C_{1-6}alkyl ester.

Compound (II) can be produced by the method shown in, for example, JPA-H9(1997)-100283, etc.

In this method, Compound (III) in the free state or in the form of a salt or reactive derivative thereof can be used as an agent for acylating the amino group at the 7-position of Compound (III). Examples of the salts of Compound (III) includes inorganic basic salts and organic basic salts. Examples of inorganic basic salts include alkali metal salts (e.g. sodium salt and potassium salt) and alkaline earth metal salts (e.g. calcium salt); examples of the organic basic salts include trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt and quinoline salt.

In this method, the compound (III) as it is, its salt or its reactive derivative is used as an acylating agent for acylation of the amino group at the 7-position of amino compound. Examples of the salt of compound (III) include an inorganic base salt and an organic base salt. Examples of the inorganic base salt include alkali metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g., calcium salt, etc.), etc., and examples of the organic base salt include trimethylamine salt, triethylamine salt, tert-butyl dimethylamine salt, dibenzyl methylamine salt, benzyl dimethylamine salt, N,N-dimethyl aniline salt, pyridine salt, quinoline salt etc. Examples of the reactive derivative of the carboxylic acid (III) include, for example, acid halides, acid azides, acid anhydrides, mixed acid anhydrides, active amides, active esters, active thio esters, etc. Examples of the acid halides include, for example, acid

chloride, acid bromide, etc.; examples of the mixed acid anhydrides include mono-C_{1-6}alkyl-carbonic acid mixed acid anhydrides (e.g. mixed acid anhydride of free acid and monomethylcarbonic acid, monoethylcarbonic acid, mono-isopropylcarbonic acid, mono-isobutylcarbonic acid, mono-tert-butylcarbonic acid, mono-benzylcarbonic acid, mono-(p-nitrobenzyl)carbonic acid, mono-allylcarbonic acid, etc.), a C_{1-6} aliphatic carboxylic acid mixed acid anhydride (e.g. mixed acid anhydride of free acid and acetic acid, trichloroacetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid, etc.), a C_{7-12} aromatic carboxylic acid mixed acid anhydride (e.g. mixed acid anhydride of free acid and benzoic acid, p-toluic acid, p-chloro benzoic acid, etc.), organic sulfonic acid mixed acid anhydrides (e.g. mixed acid anhydride of free acid and methanesulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) etc.; examples of the active amide include an amide with a nitrogen-containing heterocyclic compound (acid amide of a free acid and, for example, pyrazole, imidazole, benzo triazole, etc., these nitrogen-containing heterocyclic compound may be substituted with a C_{1-6}alkyl group (e.g., methyl, ethyl, etc.), a C_{1-6}alkoxy group (e.g., methoxy, ethoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), an oxo group, a thioxo group, a C_{1-6}alkylthio group (e.g., methylthio, ethylthio, etc.), etc.), etc.

As an active ester, all the active esters used in the field of the synthesis of β-lactam and peptide may be used. Examples of the active ester include, for example, an organic phosphoric acid ester (e.g. di-ethoxyphosphoric acid ester, di-phenoxyphosphoric acid ester, etc.), p-nitrophenyl ester, 2,4-di-nitrophenyl ester, cyanomethyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester, N-hydroxy phthalimide ester, 1-hydroxy benzotriazole ester, 6-chloro-1-hydroxybenzotriazole ester, 1-hydroxy-1H-2-pyridone ester, etc. Examples of the active thio ester include an ester of the acid with an aromatic

heterocyclic thiol compound (e.g. 2-pyridylthiol ester, 2-benzothiazolylthiol ester, etc., which heterocyclics may be substituted with a C_{1-6}alkyl group (e.g. methyl, ethyl, etc.), a C_{1-6}alkoxy group (e.g., methoxy, ethoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, etc.), a C_{1-6}alkyl-thio group (e.g., methylthio, ethylthio, etc.), etc.).

The Compound (III) may easily be produced by a known method (e.g. a method shown in JPA S60(1985)-231684, JPA S62(1987)-149682, EP0590681, etc.) or a method similar to the known method. The reaction derivative of Compound (III) can be reacted with Compound (II) after isolation from the reaction mixture, and the reaction mixture containing the reactive derivative of Compound (III) can also be used for the reaction with Compound (II). When Compound (III) is used in the form of a free acid or a salt, a pertinent condensing agent is used. Excamples of the condensing agent include, for example, a N,N'-di-substituted carbodiimide such as N,N'-di-cyclohexylcarbodiimide, etc., an azolide reagent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, etc., a dehydrating agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, an alkoxy-acetylene, etc., a 2-halogeno pyridinium salt such as 2-chloropyridiniummethyl iodide, 2-fluoropyridiniummethyl iodide, etc. When these condensing agents are used, the reaction proceeds through a reactive derivative of Compound (III). The reaction is usually carried out in a solvent which does not interfere with the reaction. Examples of the solvent include, for example, an ether such as dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisoprpyl ether, ethylene glycol-dimethyl ether, etc., an ester such as ethyl formate, ethyl acetate, acetic acid·n-butyl, etc., a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, trichlene, 1,2-dicholoroethane, etc., a hydrocarbon such as n-hexane, benzene, toluene, etc., an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamido, etc., a ketone such as acetone, methylethylketone, methylisobutylketone, etc., a nitrile such as acetonitrile, propionitrile, etc., dimethylsulfoxide, sulfolane, hexamethylphosphoramide, water,

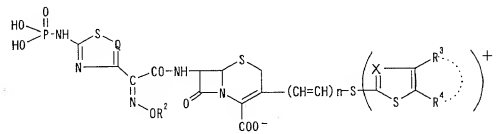
etc. These solvents may be used alone or in combination of two or more.

The amount of Compound (III) used is usually 1 to 5 moles, preferably about 1 to 2 moles per mole of Compound (II). The reaction is usually conducted in a temperature of from about-80 to 80℃, preferably from about-40 to 50℃, more preferably from about-30 to 30℃. The reaction time varies depending upon the kind of Compound (II) and Compound (III), the kind of solvent used (ratio of a solvent in case of using a mixed solvent) and the reaction temperature, and is usually about 1 minute to 72 hours, preferably about 15 minutes to 3 hours. When an acid halide is used as the acylating agent, the reaction may be carried out in the presence of a acid scavenger in order to eliminate from the reaction system a hydrogen halide formed by the reaction.

Examples of the acid scavenger include, for example, an inorganic base such as sodium carbonate, potassium carbonate, calucium carbonate, sodium hydrogencarbonate, etc., a tertiary amine such as triethylamine, tri-(n-propyl)amine, tri-(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methyl piperidine, N-methylpyrrolidine, N-methylmorpholine, etc., an alkylene oxide such as proylene oxide, epichlorohydrin etc., etc. In case that R^1 is a hydrogen atom and a phosphono group is introduced when reaction derivative forms, the reaction mixture containing reaction product wherein R^1 is a dihalophosphoryl group, may be deprotected by treating with water to obtain a compound (I) wherein R^1 is a phosphono group, or may be treated with an an alkanol such as methanol, ethanol, etc., to obtain a compound (I) wherein R^1 is an esterified phosphono group.

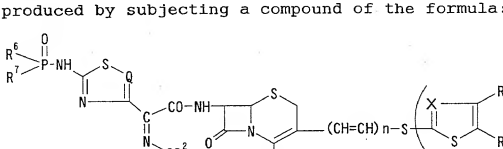
Production method (2):

Among Compound (I), a compound of the formula:



(Ia)

wherein each symbol has the meaning given above, or salt thereof (hereinafter sometimes referred to as Compound (Ia)) can be produced by subjecting a compound of the formula:



(Ib)

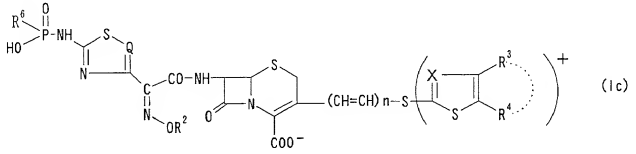
wherein R^6 and R^7 represent, the same or different, a protecting group of phosphono group, the other symbols have the meanings given above, or a salt thereof (hereinafter sometimes referred to as Compound (Ib)) to the deprotection reaction so that the protected phosphono group is deprotected.

Examples of the protecting group of a phosphono group represented by R^6 or R^7 include, for example, a halogen (e.g. chlorine atom, etc.), an alkoxy (e.g., a C_{1-3}alkoxy group such as methoxy, ethoxy, propoxy, etc.), amino, morpholino, thiomorpholino, etc.

The present method can be carried out, for example, by reacting Compound (Ib) with a halogenated trimethylsilyl such as trimethylsilyl bromide, trimethylsilyl iodide, trimethylsilyl chloride, etc., a metal halide such as sodium iodide, potassium iodide, sodium bromide, etc., an alkali metal thiocyanate such as sodium thiocyanate, potassium thiocyanate, etc., etc. The reaction is carried out in a solvent which does not interfere with the reaction, though examples of the preferable solvent include methylene chloride, dimethylacetamide, etc. The reaction temperature is not limiting and the reaction is carried out usually under cooling or under mild conditions like slight heating.

When R^6 and R^7 in Compound (Ib) are different, a protecting group of only one of R^6 and R^7 in Compound (Ib) can be removed

by selecting the reaction condition. In this case, compound of the formula:



(Ic)

wherein each symbol has the meaning given above, or salt thereof (hereinafter sometimes referred to as Compound (Ic)) is obtained.

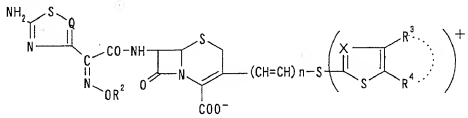
Production method (3):

Compound (Ia) can be produced, for example, by subjecting Compound (Ic) to a deprotecting reaction for removing the protecting group of the phosphono group.

The present method can be carried out, for example, by treating Compound (Ic) with an acid. The acid may be an organic acid or an inorganic acid. Preferable examples of the acid include, for example, formic acid, sulfuric acid, trifluoroacetic acid, benzenesulfonic acid, nitric acid, P-toluenesulfonic acid, hydrochloric acid, etc. More preferable examples of the acid include, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acid suitable for the reaction is selected by taking the group which is hydrolyzed into consideration. The reaction can be carried out with or without a solvent. Examples of the suitable solvent include an organic solvent, water, mixed solvent thereof, etc., which is usually used as a solvent. When trifluoroacetic acid is used, the reaction is preferably carried out in the presence of anisole.

Production method (4)

Compound (I) can be produced by condensing a compound of the formula:



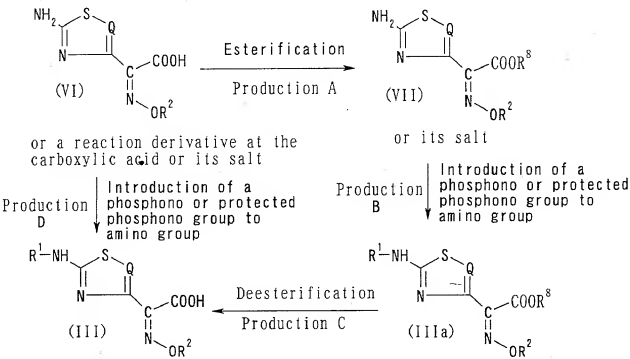
(V)

wherein each symbol has the meaning given above, or a salt thereof (hereinafter sometimes referred to as Compound (V)) and a phosphoric acid derivative.

The reaction can be carried out by using Compound (V) or a salt thereof and a phosphorus halide such as phosphorus trichloride, phosphorus pentachloride, etc., etc. The reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride, ethylene chloride, etc.), toluene, etc. The reaction temperature is not limiting and the reaction is carried out usually under cooling, an ambient temperature or under mild conditions like slight heating. In this reaction, when the reaction mixture contains Compound (I) wherein R^1 is dihalophosphoryl group, the reaction mixture may further be treated either with water to give Compound (I) wherein R^1 is phosphono group or with an alcohol (alkanol such as methanol, ethanol, etc.) to give Compound (I) wherein R^1 is an esterified phosphono group.

Compound (I) produced by the above production methods (1) to (4) can be isolated and purified by known methods, for example, extraction, column chromatography, precipitation, recrystallization, etc. On the other hand, isolated Compound (I) can be converted to a physiologically acceptable salt by a known method.

The method for producing the starting compound (III) is explained as follows :



Production A

In the above formulas, R^8 is the ester part of the esterified carboxylic group represented by the formula: CO_2R^8.

A compound of the formula (VII) or salt (hereinafter referred to sometimes as Compound (VII)) can be produced by subjecting a compound of the formula (VI), its reactive derivative or its salt (hereinafter sometimes referred to as Compound (VI)) to esterification.

Examples of the preferable salts of Compound (VI) include, for example, a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), ammonium salt, an organic salt such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, di-cyclohexylamine salt, N,N'-dibenzyl amine salt, etc., etc. Preferable examples of the reactive derivatives at carboxylic acid of Compound (VI) include those mentioned for Compound (III).

Examples of the esterifying agent used in the esterification reaction include a compound of the formula:

$(R^8)_2SO_4$, R^{8a}-N_2 or R^8-X^1

wherein R^8 has the meaning given above, R^{8a} is a group removed a hydrogen atom from R^8, X^1 is hydroxy or a halogen.

Preferable examples of the halogen include chlorine, bromine,

iodine and fluorine.

In case that a sulfuric acid ester and an alkyl halide are used as the esterifying agent, while the reaction is usually carried out in a solvent such as water, acetone, methylene chloride, ethanol, ether, dimethylformamide, etc., the reaction can be carried out in any solvent which does not interfere with the reaction. The reaction is preferably carried out in the presence of the inorganic base or the organic base mentioned above. The reaction temperature is not limiting but the reaction is usually carried out under cooling or under heating which is not higher than the boiling point of the solvent used.

In case that a diazo compound is used as the esterifying agent, the reaction is usually carried out in the presence of ether, tetrahydrofuran, etc., the reaction temperature is not limiting but the reaction is usually carried out under cooling or at an ambient temperature.

Preferable examples of the salts of Compound (VII) include, an acid addition salt such an organic acid salt as acetic acid salt, maleic acid salt, tartaric acid salt, benzenesulfonic acid salt, toluenesulfonic acid salt, etc., such inorganic acid salt as hydrochloric acid salt, hydrobromic acid salt, sulfuric acid salt, phosphoric acid salt, etc.

Productions B and D

A compound of the formula (III), its reactive derivatives at the carboxylic acid or its salt (hereinafter referred to as Compound (III)) and a compound of the formula (IIIa), its reactive derivatives at the carboxylic acid or its salt (hereinafter referred to as Compound (IIIa)) can be produced by introducing a phosphono group to the amino group of Compound (VI) and Compound (VII), respectively. Preferable examples of the reactive derivatives at the carboxylic acid of Compound (VI) and Compound (VII) include those mentioned for Compound (III).

Examples of the introducing agents to be used in the introduction reaction include, an phosphorus halide such as phosphorus trichloride, phosphorus pentachloride, etc., phosphorus oxychloride, etc. The reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride,

ethylene chloride, etc.) toluene, ethyl acetate, tetrahydrofuran, etc.

In this reaction, the reaction mixture containing Compound (III) or Compound (IIIa), wherein R^1 is a dihalophosphoryl group, which is obtained by reacting Compound (VI) or Compound (VI) with the above mentioned introducing agent such as a phosphorous halide, can be treated with water to give a reaction mixture containing Compound (III) or (IIIa) wherein R^1 is a phosphono group, or can treated with an alcohol such an alkanol as methanol, ethanol, etc. to give a reaction mixture containing Compound (III) or Compound (IIIa) wherein R^0 is an esterified phosphono group.

The reaction product (III) or (IIIa) wherein R^0 is a dihalophosphoryl group can be isolated from the above mentioned reaction mixture by means of a conventional isolation method. The product can be used in the following reaction.

The reaction includes changing Compound (IIIa) to the reactive derivative at the carboxylic group.

Production C

Compound (III) can be produced by subjecting Compound (IIIa) to deesterification reaction.

Preferable examples of the salt of Compound (III) include those enumerated for Compound (VI).

The reaction is carried out by a conventional method such as hydrolysis, reduction, etc. The hydrolysis is preferably carried out in the presence of a base or an acid. Preferable examples of the base include an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide, carbonate, bicarbonate of the above mentioned metal, an trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, 1,5-di-azabicyclo[4.3.0]nona-5-ene, 1,4-di-azabicyclo[2,2,2]octane, 1,8-di-azabicyclo[5.4.0]undecane, etc.

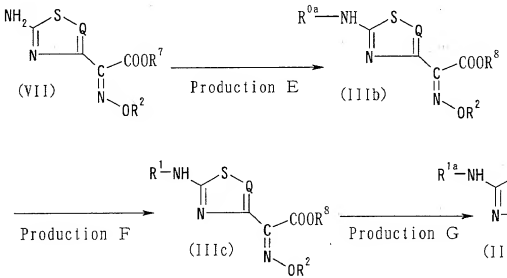
Preferable examples of the acid include an organic acid such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, etc., an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc. Trifluoroacetic acid is

preferably used in the presence of a -carbocation stabilizing agent such as anisole, etc.

While the reaction is usually carried out in water, methylene chloride, tetrahydrofuran, an alcohol (e.g. methanol, ethanol, etc.) or a mixture thereof, a solvent which does not interfere with the reaction may be used. A liquid base or an acid may also be used as a solvent. The reaction temperature is not limiting and the reaction is carried out usually under cooling or under mild conditions like slight heating.

The reduction can be applied to deprotection of a protecting group of the ester, such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloro ethyl, etc. As the method of the reduction which is applied to the deesterification reaction, there may be mentioned a method using a metal such as zinc, zinc amalgam, etc., or a chromium compound salt such as chromous chloride salt, chromous acetate salt, etc., in combination with an organic or inorganic salt such as acetic acid, propionic acid, hydrochloric acid, etc., and a catalytic reduction method using a metal catalyst such as palladium-carbon, etc.

The production of a starting compound that is a compound of the formula (IIId) or its reactive derivative (hereinafter referred to as Compound (IIId)) is as follows.



[wherein R^{0a} is a dihalophosphoryl group, R^{1a} is a phosphono group which may be protected. (The definition of R^{1a} is the same as that of R^1, but R^{1a} and R^1 may be the same as or different from each other.

Production E

A compound of the formula (IIIb), its reactive derivative or its salt (hereinafter referred to as Compound (IIIb)) can be produced by subjecting Compound (VII) to a reaction in which a dihalophosphoryl group is introduced to the amino group of Compound (VII). The reaction can be carried out in a similar manner to Production B or Production D.

Production F

A compound of the formula (IIIc), its reactive derivative or its salt (hereinafter referred to as Compound (IIIc)) can be produced by subjecting Compound (IIIb) to a reaction in which the dihalophosphoryl group is converted to a phosphono group other than dihalophosphoryl group. The reaction can be carried out by subjecting Compound (IIIb) to an esterification reaction and/or amidation reaction.

The esterification reaction is carried out by reacting Compound (IIIb) with an alcohol. Preferable examples of the alcohol include methanol, ethanol, propanol, butanol, etc. The amidation reaction can be carried out by reacting Compound (IIIb) with an amine. Preferable examples of the amine include ammonia, a primary amine such as methylamine, ethylamine, etc., a secondary amine such as morpholine, dimethylamine, etc., etc.

While the esterification reaction or amidation reaction is usually carried out in a solvent such as a halogenated alkylene (e.g. methylene chloride, ethylene chloride, etc.), tetrahydrofuran, water, etc., it can be carried out in any solvent which does not interfere with the reaction. The reaction temperature is not limiting though the reaction is carried out usually under cooling or an ambient temperature.

Production G

Compound (IIId) can be produced by subjecting Compound (IIIc) to deesterification reaction.

The reaction is carried out in a similar manner to that of Production C.

In the reactions mentioned above, when the starting compound has an amino group and/or a carboxyl group, these groups may be protected by a protecting group which is conventionally used in

the field of peptide chemistry, and the protecting group may be removed after the reaction.

Examples of the protecting group for the amino group include, for example, a formyl group, a C_{1-6}alkyl-carbonyl group (for example, acetyl, ethylcarbonyl, etc.), a benzyl group, a tert-butyloxycarbonyl group, a benzyloxycarbonyl group, a 9-fluorenyl methyloxycarbonyl group, an allyloxycarbonyl group, a phenylcarbonyl group, a C_{1-6}alkyl-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, etc.), a C_{7-10}aralkyl-carbonyl group (for example, benzylcarbonyl, etc.), a trityl group, phthaloyl group, a N,N-dimethylaminomethylene group, etc. These groups may be substituted by 1 to 3 of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a nitro group, etc. Examples of the protecting group for the carboxyl group include, for example, a C_{1-6}alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), a phenyl group, a silyl group, a benzyl group, an allyl group, etc. These groups may be substituted by one to three of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a nitro group, etc.

Examples of the protecting group for the hydroxy include, for example, a methoxy methyl group, an allyl group, a tert-butyl group, a C_{7-10}aralkyl group (for example, benzyl, etc.), formyl group, a C_{1-6}alkyl-carbonyl group (for example, acetyl, ethylcarbonyl, etc.), a benzoyl group, a C_{7-10}aralkyl-carbonyl group (for example, benzylcarbonyl, etc.), a pyranyl group, a furanyl group, a tri-alkyl silyl group, etc. These groups may be substituted by 1 to three of a halogen atom (for example, fluorine, chlorine, bromine, etc.), a C_{1-6}alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), a phenyl group, a C_{7-10}aralkyl group (for example, benzyl, etc.), a nitro group, etc.

As the method for the deprotection of these protecting group, a method using, for example, an acid, a base, reduction, ultraviolet ray, hydrazine, phenyl hydrazine, sodium N-methyl di-thiocarbamate, tetrabutyl ammonium fluoride, palladium acetate, etc. can be applied, using known or similar methods.

When a compound is obtained as a free form in each reaction process, the compound can be converted to its salt, and when the compound is obtained as a salt, it can be converted to its free form or to an another salt.

Compound (I) thus obtained can be isolated from the reaction mixture and purified by a known procedure such as phase transfer, concentration, solvent extraction, fractional distillation, crystallization, recrystallization, chromatography, etc. When Compound (I) of the present invention exists in the form of diastereomer, conformer, etc., Compound (I) can be isolated and purified by a isolation procedure or a purification procedure mentioned above, if desirable. When Compound (I) is a racemate, (d)-form and (l)-form of Compound (I) can be isolated by a usual optical resolution procedure.

Compound (I) of the present invention has a solubility higher than that of the corresponding compound having an aminothiazolyl group wherein the amino group is free form (that is Compound (I) wherein R^1 is an amino group), and Compound (I) of the present invention in vivo, gives a corresponding compound having an aminothiazolyl group by removing group R^1. Further Compound (I) is superior in an anti-bacterial activity to a compound having aminothiazolyl group.

The compound (I) of this invention has broad spectrum antibacterial activity and low toxicity, and can be used safely for prophylaxis and therapy of various diseases, in man and mammals (e.g. mouse, rat, rabbit, dog, cat, cow and pig), caused by pathogenic bacteria, for example, respiratory infection and urinary tract infection. Characteristic features of the antibacterial spectrum of the antibacterial compound (I) are as follows, among others :

(1) showing a remarkably high activity against a variety of Gram-negative bacteria,

(2) having high activities against Gram-positive bacteria (e.g. Staphylococcus aureus and Corynebacterium diphtheriae),

(3) having high activities against methicillin-resistant Staphylococcus aureus (MRSA), and

(4) having high activities also against a number of β-

lactamase-producing Gram-negative bacteria (e.g. genera Escherichia, Enterobacter, Serratia and Proteus).

The anti-bacterial compound (I) of the present invention has superior stability and effectiveness of anti-bacterial activity in comparison with Compound (V).

The compound (I) of this invention can be administered, like known penicillin preparations or cephalosporin preparations, non-orally or orally as injectable preparations, capsules, tablets or granular preparations (injectable preparations are especially preferable). The daily dose ranges from 0.5 to 80 mg, preferably from 2 to 40 mg relative to 1 kg of the body weight of a man or an animal infected with pathogenic bacteria as described above, which may be administered in two or three divided doses.

Though the drug of the present invention may comprise only Compound (I) itself, it is usually prepared by a conventional manner by using a proper amount of pharmaceutically acceptable carriers, diluents and bulking agents, etc. which are selected from exipients (for example, calucium carbonate, kaolin, sodium hydrogencarbonate, lactose, D-mannnitol, starch, crystaline cellulose, talc, fine granulated sugar, porous substance, etc.), binders (for example, dextrin, gums, α-starch, gelatine, hydroxypropylcellulose, hydroxy propyl methyl cellulose, pullulan, etc.), thickeners (for example, a natural gum, a cellulose derivative, an acrylic acid derivative, etc.), disintegrators (for example, carboxymethylcellulose calcium, crosscarmelose sodium, crospovidone, a low-substituted hydroxypropylcellulose, partly pregelatinized starch, etc.), solvents (for example, water for injection, alcohol, propyleneglycol, Macrogol, sesame oil, corn oil, etc.), dispersants (for example, Tween 80, HCO60, poly ethylene glycol, carboxymethylcellulose, sodium alginate, etc.), solbilizing agents (for example, polyethylene glycol, propyleneglycol, D-mannnitol, benzoic acid benzyl, ethanol, tris amino methane, tri-ethanolamine, sodium carbonate, citric acid sodium, etc.), suspending agents (for example, stearyl triethanolamine, sodium laurylsulfate, benzalkonium chloride, polyvinylalcohol,

polyvinylpyrolidone, hydroxymethylcellulose, etc.), soothing agents (for example, benzyl alcohol, etc.), isotonic agents (for example, sodium chloride, glycerin, etc.), buffer agents (for example, phosphoric acid salt, acetic acid salt, carbonic acid salt, citric acid salt, etc.), lubricants (for example, magnesium stearate, calcium stearate, talc, starch, sodium benzoate, etc.), coloring agents (for example, tar pigment, caramel, ferric oxide, titanium oxide, riboflavins, etc.), corrigents (for example, a sweetning agent, a perfume, etc.), stabilizers (for example, sodium sulfite, ascorbic acid, etc.) and preservatives (for example, paraben, sorbic acid, etc.), etc.

The pharmaceutical composition of the present invention which may contain pharmaceutically acceptable carriers, diluents, bulking agents, etc., mentioned above contains an effective amount of Compound (I) of the present invention for the treatment and prevention. The amount of Compound (I) contained in the pharmaceutical preparation of the present invention is usually 0.1 to 100 weight % of the pharmaceutical preparation. The pharmaceutical preparation of the present invention may contain pharmaceutically active ingredients other than Compound (I)(e.g. antitumor agents, etc., mentioned below). The amount of the pharmaceutically active ingredient other than Compound (I) is not limited as long as the aim of the present invention can be achieved. Examples of the preparation includes tablets (including a sugar-coated tablet, a film-coated tablet), pills, capsules (including microcapsule), granules, fine granules, powders, drop infusions, syrups, emulsions, suspensions, injections, inhalations, ointments, suppositories, troches, cataplasms, sustained release preparations, etc. These preparation can be prepared by a conventional method (e.g., a method shown in The Pharmacopoeia of Japan The Twelfth Edition, etc.).

As carriers for injectable preparations, use is made of, for example, distilled water or a physiological saline solution. Carriers for capsules, powdery preparations, granular preparations or tablets are used as a mixture with known pharmaceutically acceptable excipients (e.g. starch, maltose,

sucrose, calcium carbonate or calcium phosphate), binders (e.g. starch, gum arabic, carboxymethyl cellulose, hydroxypropyl cellulose or crystalline cellulose), lubricants (e.g. magnesium stearate or talc) and disintegrants (e.g. carboxymethyl calcium and talc).

The compound (I) of this invention can be administered, like known penicillin preparations or cephalosporin preparations, non-orally or orally as injectable preparations, capsules, tablets or granular preparations (injectable preparations are especially preferable). The daily dose ranges from 0.5 to 80 mg, preferably from 2 to 40 mg relative to 1 kg of the body weight of a man or an animal infected with pathogenic bacteria as described above, which may be administered in two to three divided doses.

As carriers for injectable preparations, use is made of, for example, distilled water or a physiological saline solution. Carriers for capsules, powdery preparations, granular preparations or tablets are used as a mixture with known pharmaceutically acceptable excipients (e.g. starch, maltose, sucrose, calcium carbonate or calcium phosphate), binders (e.g. starch, gum arabic, carboxymethyl cellulose, hydroxypropyl cellulose or crystalline cellulose), lubricants (e.g. magnesium stearate or talc) and disintegrants (e.g. carboxymethyl calcium and talc). Incidentally, the medicinal composition and antibacterial composition employed in the present specification may contain the compound (I) alone, or contain, among others, such carriers as set forth above, or contain a proper amount of any other adequate antibacterial compound.

The present invention will be illustrated in further detail in the following Working Examples, which are mere examples and do not limit this invention, and may be modified within the range not deviating from the scope of this invention.

Elutions in the column chromatography conducted in Working Examples were carried out while monitoring with TLC (Thin Layer Chromatography). In the TLC monitoring, as the TLC plate, use was made of $60F_{254}$ manufactured by Merck & Co., Inc., as the developing solvent, use was made of the same solvent as employed

for eluting in the column chromatography, and the detection was conducted with a UV detector. The silica gel (70 to 230 mesh) for the column was Kieselgel 60 manufactured by Merck & Co. Inc. ODS-AM is produced by YMC Co. Ltd., Dowex50W is produced by The Dow Chemical Company and Diaion HP-2OSS and SP-207 are produced by Mitsubishi Chemical Industries, Ltd.

NMR spectra were measured using tetramethylsilane as an internal or external standard with a spectrometer Gemini 200 and all delta values were expressed in ppm. The value shown in () for a mixed solvent is a mixing ratio in volume of constituent solvents. The percent (%) for a solution indicates the number of grams in 100 ml of the solution. And, the symbols in Reference Examples and Working Examples have the following meaning.

s : singlet
d : doublet
t : triplet
q : quartet
ABq : AB type quartet
dd : double doublet
m : multiplet
bs : broad singlet
J : coupling constant

Working Example 1

7 β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, the pH of a solution of 7 β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (1.55g) in a mixture of THF (50ml) and H_2O (50ml) was adjusted to 7.4 with 0.6M $NaHCO_3$. To the solution was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (3.69g), and the mixture was stirred at 5℃ for 10 minutes while maintaining the pH to 7.2 to 7.3 by addition of 0.6M $NaHCO_3$. A solution of sodium acetate (861mg) in H_2O (10ml) was poured into the reaction mixture, and the resulting mixture was stirred at room temperature for 2.5 hours. During the stirring, the pH of the mixture was maintained above 4.5 by the occasional addition of 0.6M $NaHCO_3$

(total volume 56ml). After the pH of the mixture was adjusted to 3.0 with 1N HCl (4ml), the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (800ml) and purified by MCI gel HP-20SS column chromatography (500ml: eluents = H_2O 1.5L, 10% aq EtOH 0.5L, 20% aq EtOH 1.5L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (1.64g).

^{1}H NMR (D_2O) δ : 1.33 (3H,t,J=7.2Hz), 3.56, 3.94 (2H,ABq,J=17.2Hz), 4.34 (3H,s), 4.35 (2H,q,J=7.2Hz), 5.38 (1H,d,J=5Hz), 5.90 (1H,d,J=5Hz), 8.34, 8.72 (each2H,d,J=6.6Hz), 8.51 (1H,s); IR (KBr, cm^{-1}) : 3055, 1778, 1682, 1643, 1520, 1385, 1190, 1038.

Working Example 2

7 β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (1.54g) obtained in Working Example 1 was dissolved in a solution of $NaHCO_3$ (378mg) in H_2O (16ml). The solution was subjected to ODS-AM column chromatography (450ml: eluents = 1N HCl 4.5ml, H_2O 1.0L, 5% aq acetonitrile 0.5L, 20% aq acetonitrile 0.25L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (431mg).

Anal Calcd for $C_{22}H_{21}N_8O_8PS_4 \cdot 2.0H_2O$: C, 36.66; H, 3.50; N, 15.55. Found: C, 36.70; H, 3.94; N, 15.53.

Working Example 3

7 β-[2(Z)-Fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, the pH of a solution of 7 β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (1.42g) in a mixture of THF (50ml) and H_2O (50ml) was adjusted to 7.5 with 0.6M $NaHCO_3$ (12ml). To the solution was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoxyiminoacetyl chloride (3.41g), and the mixture was stirred at 5℃ for 10 minutes while maintaining the pH to 7.2 to 7.5 by addition of 0.6M $NaHCO_3$ (24ml).

A solution of sodium acetate (787mg) in H_2O (20ml) was poured into the reaction mixture, and the resulting mixture was stirred at room temperature for 3 hours. After the pH of the mixture was adjusted to 3.0 with 1N HCl (3.4ml), the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (750ml) and purified by MCI gel HP-20SS column chromatography (500ml: eluents = H_2O 1.5L, 10% aq EtOH 0.5L, 20% aq EtOH 1.5L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (0.96g).

^{1}H NMR (D_2O) δ : 3.57, 3.94 (2H,ABq,J=17.4Hz), 4.34 (3H,s), 5.40 (1H,d,J=4.8Hz), 5.85 (2H,d,J=55Hz), 5.93 (1H,d,J=4.8Hz), 8.34, 8.72 (each2H,d,J=6.4Hz), 8.51 (1H,s); IR (KBr, cm^{-1}) : 3055, 1781, 1677, 1642, 1523, 1364, 1189, 1071.

Working Example 4

7 β-[2(Z)-Fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (0.96g) obtained in Working Example 3 was dissolved in a solution of $NaHCO_3$ (234mg) in H_2O (15ml). The solution was subjected to ODS-AM column chromatography (450ml: eluents = 1N HCl 3.06ml, H_2O 1.0L, 20% aq acetonitrile 0.25L, 30% aq acetonitrile 0.6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (600mg).

Anal Calcd for $C_{21}H_{18}N_8O_8FPS_4 \cdot 2.0H_2O$: C, 34.81; H, 3.06; N, 15.46; P, 4.27. Found: C, 34.84; H, 3.28; N, 15.43; P, 4.18.

Working Example 5

7 β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Under ice-cooling, 0.6M $NaHCO_3$ (34ml) was added to a solution of 7 β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate hydrochloride (3.0g) in a mixture of THF (150ml) and H_2O (150ml). To the solution were added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (4.76g) and 0.6M $NaHCO_3$ (23ml) successively. The resulting mixture was stirred at 5℃ for 15

minutes and then at room temperature for 2 hours. Under ice-cooling, the pH of the reaction mixture was adjusted to 5.0 with 1N NaOH, and the mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (2.5L), and the pH of the solution was adjusted to 3.0 with 1N HCl. The mixture was purified by MCI gel SP-207 column chromatography (750ml: eluents = H_2O 4L, 15% aq EtOH 6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (2.6g).

^{1}H NMR (DMSO-d_6) δ : 1.23 (3H,t,J=7Hz), 3.56, 3.94 (2H,ABq,J=17Hz), 4.17 (2H,q,J=7Hz), 4.33 (3H,s), 5.30 (1H,d,J=5Hz), 5.90 (1H,dd,J=5&8.8Hz), 8.50, 8.97 (each2H,d,J=6.4Hz), 8.98 (1H,s), 9.22 (1H,m), 9.69 (1H,d,J=8.8Hz).

Working Example 6

7 β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

The crude lyophilized compound (1.24g) obtained in Working Example 5 was dissolved in H_2O (13ml) containing 1N NaOH (3.24ml). The solution was subjected to ODS-AM column chromatography (450ml: eluents = H_2O). The fractions containing sodium salt form of the desired compound were passed through Dowex 50×8 column (H form, 20 to 50mesh, 100ml). The eluent was concentrated under reduced pressure, and the concentrate was lyophilized to give the titled compound (377mg).

Anal Calcd for $C_{22}H_{21}N_8O_8PS_4 \cdot 3.5H_2O$: C, 35.29; H, 3.77; N, 14.97. Found: C, 35.26; H, 3.45; N, 14.99.

^{1}H NMR (DMSO-d_6) δ : 1.24 (3H,t,J=7Hz), 3.54, 3.94 (2H,ABq,J=17Hz), 4.20 (2H,q,J=7Hz), 4.33 (3H,s), 5.30 (1H,d,J=5.2Hz), 5.89 (1H,dd,J=5.2&8.6Hz), 8.51, 8.98 (each2H,d,J=5.6Hz), 8.98 (1H,s), 9.17 (1H,m), 9.69 (1H,d,J=8.6Hz).

Working Example 7

7 β-[2(Z)-Ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate

Trimethylsilylacetamide (919mg) was added to a suspension of 7 β-amino-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-

cephem-4-carboxylate hydrochloride (240mg) in dichloromethane (4ml), and the mixture was stirred at room temperature for 40 minutes. To the mixture was added portionwise 2-(5-dichlorophosphorylamino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetyl chloride (351mg) under cooling at -15℃, and the mixture was stirred at -15 to -5℃ for 1 hour. After concentration of the reaction mixture under reduced pressure, the concentrate was diluted with H_2O (150ml). Under ice-cooling, the pH of the mixture was adjusted to 5.0 with 1N NaOH. The mixture was diluted with H_2O (200ml), and the pH of the mixture was adjusted to 3.0 with 1N HCl. The mixture was purified by MCI gel SP-207 column chromatography (180ml: eluents = H_2O 0.5L, 15% aq EtOH 0.6L). The fractions containing the desired compound were concentrated under reduced pressure, and the concentrate was lyophilized to give the crude titled compound (100mg).

^{1}H NMR (DMSO-d_6) δ : 1.23 (3H,t,J=7Hz), 3.56, 3.94 (2H,ABq,J=17Hz), 4.17 (2H,q,J=7Hz), 4.33 (3H,s), 5.30 (1H,d,J=5Hz), 5.90 (1H,dd,J=5&8.8Hz), 8.50, 8.97 (each2H,d,J=6.4Hz), 8.98 (1H,s), 9.22 (1H,m), 9.69 (1H,d,J=8.8Hz).

Working Example 8

The lyophilized 7 β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate (300mg equivalent), obtained in Working Example 6, was dissolved in saline, the pH was adjusted to 6.0, and saline was added to make the total volume 5ml (60mg equivalent/ml).

Experiment 1

The lyophilized 7 β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate , obtained in Working Example 6, was dissolved in mouse plasma to prepare 10mg equivalent/ml solution. After incubation at 37℃, the transformation rate into 7 β-[2(Z)-ethoxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate (amino form) was measured. The transformation rates in 30 minutes and 1 hour were as follows:

30 minutes 35%

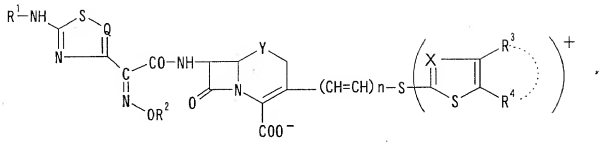
1 hour 62%

INDUSTRIAL APPLICABILITY

The cephem compound (I) has a broad antibacterial spectrum and an excellent antibacterial activity against Gram-negative bacteria and Gram-positive bacteria including Staphylococcus aureus and MRSA, and its useful for treatment or prevention of infectious diseases caused by these bacteria. And the compound (I) has a relatively high solubility in water, and can be advantageously used as injection.

Claims

1. A compound of the formula:



wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, salt or ester thereof.

2. A compound as claimed in claim 1, wherein R^1 is a phosphono group which may be protected.

3. A compound as claimed in claim 1, wherein R^1 is phosphono, dialkoxy-phosphoryl, O-alkyl-phosphono, diaminophosphoryl, (amino)(hydroxy)phosphoryl, (alkoxy)(morpholino)phosphoryl or dihalophosphoryl.

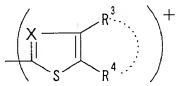
4. A compound as claimed in claim 1, wherein R^1 is a phosphono group.

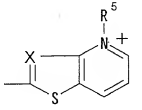
5. A compound as claimed in claim 1, wherein Y is S.

6. A compound as claimed in claim 1, wherein R^2 is a C_{1-6}alkyl group which may be substituted or a C_{3-5}cycloalkyl group.

7. A compound as claimed in claim 1, wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom.

8. A compound as claimed in claim 1, wherein the group of the formula:


is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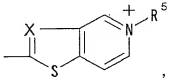
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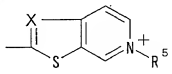
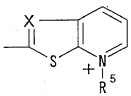


or



wherein R^5 is a hydrocarbon group which may be substituted.

9. A compound as claimed in claim 1, wherein Q is a nitrogen atom.

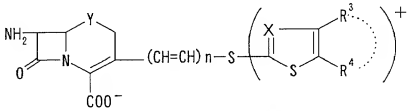
10. A compound as claimed in claim 1, wherein X is a nitrogen atom.

11. A compound according to the above (1), wherein n is 0.

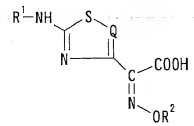
12. A compound according to the above (1), which is 7β-[2(Z)-ethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester or its salt.

13. A compound according to the above (1), which is 7β-[2(Z)-fluoromethoxyimino-2-(5-phosphonoamino-1,2,4-thiadiazole-3-yl)acetamido]-3-[4-(1-methyl-4-pyridinio)-2-thiazolylthio]-3-cephem-4-carboxylate, its ester or its salt.

14. A method for producing a compound as claimed in claim 1, which comprises reacting a compound of the formula:

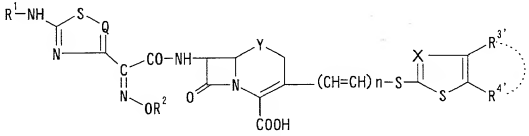


wherein each symbol has the meaning given above, its ester or its salt, with a compound of the formula:



wherein each symbol has the meaning given above, its salt or its reactive derivative, if necessary, followed by converting R^1 to a phosphono group.

15. A method for producing a compound as claimed in claim 1, which comprises subjecting a compound of the formula:



(IV)

wherein one of $R^{3'}$ and $R^{4'}$ is a pyridyl group which may be substituted, and the other is a hydrogen atom or a hydrocarbon group which may be substituted, or $R^{3'}$ and $R^{4'}$, taken together, represent a nitrogen-containing heterocyclic ring which may be substituted, and the other symbols have the meanings given above, its ester or its salt to the reaction in which quaternalized-ammonium is formed, if necessary, followed by converting R^1 to a phosphono group.

16. A pharmaceutical composition containing the compound as claimed in claim 1.

17. A pharmaceutical composition containing the compound shown in claim 1 and at least one of pharmaceutically acceptable carriers, diluents and bulking agents.

18. A pharmaceutical composition as claimed in claim 16, which is an anti-bacterial composition.

19. A pharmaceutical composition as claimed in claim 16 which is an anti-MRSA agent.

20. A pharmaceutical composition as claimed in claim 16, which is an injectable composition.

21. Use of the compound as claimed in claim 1 for producing a pharmaceutical composition.

22. Use as claimed in claim 21, wherein the pharmaceutical composition is an antibacterial agent.

23. Use as claimed in claim 21, wherein the pharmaceutical composition is an anti-MRSA agent.

24. Use as claimed in claim 21, wherein the pharmaceutical composition is an injectable composition.

25. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 to a patient suffering from the bacterial infection.

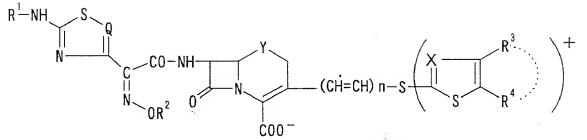
26. A method for treating a bacterial infection which comprises administering an effective amount of a compound as claimed in claim 1 together with at least one of pharmaceutically acceptable carriers, diluents and excipients to a patient suffering from the bacterial infection.

27. A method as claimed in claim 25, wherein the bacterial infection is a MRSA infection.

28. A method as claimed in claim 25, wherein the compound is administered by injection.

Abstract

A novel cephem compound of the formula:



wherein R^1 is a phosphono group or a group convertible to a phosphono group; R^2 is a hydrogen atom or a group having a linkage through a carbon atom; each of Q and X is a nitrogen atom or CH; Y is S, O or CH_2; n is 0 or 1; one of R^3 and R^4 is a pyridinium group which may be substituted and the other is a hydrogen atom or hydrocarbon group which may be substituted, or R^3 and R^4 taken together may form a quaternalized nitrogen-containing heterocyclic ring which may be substituted, or its ester or its salt, which has a superior anti-bacterial activity, stability, absorbability, etc., a production thereof and a pharmaceutical composition containing it, is provided.

PTO/SB/106 (8-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

As a below named inventor, I hereby declare that:

私の住所、私書箱、国籍は下記の私の氏名の後に記載された通りです。

My residence, post office address and citizenship are as stated next to my name.

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者であると（下記の名称が複数の場合）信じています。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Phosphonocephem Derivatives, Their Production and Use

上記発明の明細書（下記の欄でxⅡがついていない場合は、本書に添付）は、

the specification of which is attached hereto unless the following box is checked:

☐ __月__日に提出され、米国出願番号または特許協定条約国際出願番号を_____とし、（該当する場合）_____ に訂正されました。

☒ was filed on December 17, 1998 as United States Application Number or PCT International Application Number PCT/JP98/05709 and was amended on _____ (if applicable).

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第３７編第１条５６項に定義されるとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

PTO/SB/106 (6-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Japanese Language Declaration
(日本語宣言書)

私は、米国法典第３５編１１９条 (a) - (d) 項又は３６５条 (b) 項に基き下記の、米国以外の国の少なくとも一ヵ国を指定している特許協力条約３６５ (a) 項に基ずく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

I hereby claim foreign priority under Title 35, United States Code, Section 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Not Claimed 優先権主張なし
9-351499	Japan	19/12/1997	☐
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	☐

私は、第３５編米国法典１１９条 (e) 項に基いて下記の米国特許出願規定に記載された権利をここに主張いたします。

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filing Date) (出願日)

私は、下記の米国法典第３５編１２０条に基いて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約３６５条 (c) に基ずく権利をここに主張します。また、本出願の各請求範囲の内容が米国法典第３５編１１２条第１項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第３７編１条５６項で定義された特許資格の有無に関する重要な情報について開示義務があることを認識しています。

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)
(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

私は、私自身の知識に基ずいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じるところに基ずく表明が全て真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第１８編第１００１条に基ずき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は表に許可された特許の有効性が失われることを認識し、よってここに下記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

PTO/SB/106 (8-96)
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Japanese Language Declaration
(日本語宣言書)

委任状： 私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。（弁護士、または代理人の氏名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith *(list name and registration number)*

Philippe Y. RIESEN (Reg. No. 35,657), Miriam SOHN (Reg. No. 35,368) (2)

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唯一または第一発明者名	Full name of sole or first inventor Tomoyasu ISHIKAWA
発明者の署名 日付	Inventor's signature Date Tomoyasu Ishikawa May 24, 2000
住所 4-18, Asahigaoka 2-chome, Otsu-shi, SHIGA 520-0052 JAPAN	Residence JPX
国籍	Citizenship Japan
私書箱 Takeda Chemical Industries, Ltd. (IPD) 17-85, Jusohonmachi 2-chome, Yodogawa-ku, OSAKA 532-8686 JAPAN	Post Office Address
第二共同発明者	Full name of second joint inventor, if any Shohei HASHIGUCHI
第二共同発明者 日付	Second inventor's signature Date Shohei Hashiguchi May 24, 2000
住所 10-17, Nakasakurazuka 1-chome, Toyonaka-shi, OSAKA 560-0881JAPAN	Residence JPX
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（第三以降の共同発明者についても同様に記載し、署名をすること）

(Supply similar information and signature for third and subsequent joint inventors.)

[x] 1 attached sheet will follow

Attached Sheet to the Declaration

第三共同発明者		Full name of third joint inventor, if any Yuji IIZAWA	
発明者の署名	日付	Third inventor's signature Yuji Iizawa	date May 24, 2000
住所		Residence 13-5-403, Kamimachida, Morimotocho, Muko-shi, KYOTO 617-0003 JAPAN JPX	
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第四共同発明者		Full name of fourth joint inventor, if any	
発明者の署名	日付	Fourth inventor's signature	date
住所		Residence	
国籍		Citizenship	
私書箱		Post Office Address	
第五共同発明者		Full name of fifth joint inventor, if any	
発明者の署名	日付	Fifth inventor's signature	date
住所		Residence	
国籍		Citizenship	
私書箱		Post Office Address	
第六共同発明者		Full name of sixth joint inventor, if any	
発明者の署名	日付	Sixth inventor's signature	date
住所		Residence	
国籍		Citizenship	
私書箱		Post Office Address	